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ORIGINAL RESEARCH

CARDIOMETABOLIC

Association of a Low-Carbohydrate High-Fat Diet With Plasma Lipid Levels and Cardiovascular Risk

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ABSTRACT

BACKGROUND Low-carbohydrate high-fat (LCHF) diets have attracted interest for a variety of conditions. In some individuals, these diets trigger hypercholesterolemia. There are limited data on their effects on cardiovascular disease risk.

OBJECTIVES The purpose of this study was to investigate the association between LCHF dietary patterns, lipid levels, and incident major adverse cardiovascular events (MACE).

METHODS In a cohort from the UK Biobank, participants with ≥1 24-hour dietary questionnaire were identified. A LCHF diet was defined as <100 g/day and/or <25% total daily energy from carbohydrates/day and >45% total daily energy from fat, with participants on a standard diet (SD) not meeting these criteria. Each LCHF case was age- and sex-matched 1:4 to SD individuals.

RESULTS Of the 2034 LCHF and 8136 SD identified participants, 305 LCHF and 1220 SD individuals completed an enrollment assessment concurrently with lipid collection. In this cohort, low-density lipoprotein-cholesterol (LDL-C) and apolipoprotein B levels were significantly increased in the LCHF vs SD group ($P < 0.001$). 11.1% of LCHF and 6.2% of SD individuals demonstrated severe hypercholesterolemia (LDL-C >5 mmol/L, $P < 0.001$). After 11.8 years, 9.8% of LCHF vs 4.3% of SD participants experienced a MACE ($P < 0.001$). This difference remained significant after adjustment for cardiovascular risk factors (HR: 2.18, 95% CI: 1.39-3.43, $P < 0.001$). Individuals with an elevated LDL-C polygenic risk score had the highest concentrations of LDL-C on a LCHF diet. Similar significant changes in lipid levels and MACE associations were confirmed in the entire cohort and in ≥2 dietary surveys.

CONCLUSIONS Consumption of a LCHF diet was associated with increased LDL-C and apolipoprotein B levels, and an increased risk of incident MACE. (JACC Adv 2024;3:100924) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

FH = familial hypercholesterolemia

KD = ketogenic diet

LCHF = low-carbohydrate high-fat diet

LDL-C = low-density lipoprotein-cholesterol

MACE = major adverse cardiovascular events

PRS = polygenic risk score

SD = standard diet

SFA = saturated fat

TDE = total daily energy

UKBB = UK Biobank

Healthy dietary patterns are a key component of managing risk of atherosclerotic cardiovascular disease (ASCVD). In the last decade, low-carbohydrate high-fat (LCHF) diets have become increasingly popular due to their purported health benefits for a variety of conditions, including obesity and diabetes control.[1] In 2022, in a nationally weighted survey, approximately 20% of American adults, representing 51.7 million individuals, reported following a form of low-carbohydrate (LC) dietary pattern, including a ketogenic diet (KD), LC, or carb-cycling, in the previous year.[2] These are among the most frequently followed diets, with comparable prevalence to the commonly recommended Mediterranean and Dietary Approaches to Stop Hypertension diets.[2] LC diets have gained recognition in the American and European Diabetes Guidelines as dietary options for glycemic control and weight reduction, but also due to their subjective benefits on various aspects of well-being such as energy, endurance and mental clarity.[3,4]

LCHF diets typically involve restriction of carbohydrates in favor of a higher intake of fats, often from animal sources. The National Lipid Association Nutrition and Lifestyle Task Force classifies these diets based on the proportion of total daily energy (TDE) and/or absolute carbohydrate intake.[5,6] Very-low carbohydrate (VLC) high-fat diets or KDs generally limit carbohydrate intake to ≤50 g/day or ≤10% of daily caloric consumption with >70% TDE from fat, typically inducing ketosis, while LC diets restrict carbohydrates to ≤100 g/day or ≤25% TDE.[5,6]

In some cases, these dietary interventions have been described as cardioprotective due to the effects of ketone bodies on cardiac energetics and cardiomyocytes metabolism.[7] However, there remains concern about the potential effect of LCHF diets on increasing levels of atherogenic lipoproteins[5,6] and several studies have reported exacerbation of hypercholesterolemia in different populations, including healthy individuals following carbohydrate-restricted diets.[8-12] In some cases, considerable increases in low-density lipoprotein-cholesterol (LDL-C) levels have been observed, with genetic background thought to contribute to interindividual variability of lipid responses to dietary interventions.[10,13] Despite this, there are limited data on the effects of LCHF diets on risk of ASCVD. The goal of this study was to investigate the association between a LCHF dietary pattern, serum lipid levels, and incident major adverse cardiovascular events (MACE) in a population-based cohort from the UK Biobank (UKBB). We further determined if genetic variants associated with hypercholesterolemia influenced lipid levels in individuals on a LCHF diet.

METHODS

STUDY POPULATION. The UKBB is a prospective observational study of 502,546 participants aged 40 to 69 years recruited from 22 sites across the United Kingdom between March 13, 2006, and October 1, 2010, with ongoing follow-up. The UKBB protocol was approved by the Northwest Multi-Center Research Ethics Committee with study participants providing written informed consent. Access to the UKBB was granted by the UKBB Access Sub-Committee under the University of British Columbia's Application 42857. Data were analyzed from May 2022 to October 2023.

Serum lipids, cardiovascular disease (CVD)-related biomarkers, and ketone body measurements were performed as described in Supplemental Methods 1.

DIETARY ASSESSMENT. Dietary intakes were collected by a validated web-based, self-administered questionnaire (Oxford WebQ) that recorded consumption of 206 common food and 32 beverage items in the previous 24 hour (April 2009-September 2010).[14] Participants who provided an email address at recruitment were further invited to complete the 24-hour survey online on 4 separate occasions between 2011 and 2012.

From the original sample of UKBB individuals, we used data from participants having completed at least 1 dietary assessment at any point in time (Supplemental Figure 1A, entire cohort) and at baseline (Supplemental Figure 1B, subset cohort) and having provided blood samples for analyses at the time of enrollment. The subgroup cohort included mandatory completion of the 24-hour questionnaire at the initial visit to ensure that the assessment was performed at the same time as serum was collected. The total nutrient intakes from each food/beverage collected at each assessment were generated as described in Supplemental Methods 2. We calculated macronutrient consumptions (carbohydrate, protein, and fat) expressed as %TDE, determined as the daily calories derived from each macronutrient divided by the total calories for the day.

INCLUSION AND EXCLUSION CRITERIA. The participants' flow diagram is shown in Supplemental Figure 1. In the entire cohort analysis (part A), individuals were excluded if they: 1) withdrew consent; 2) were taking lipid-lowering therapy; 3) had

implausible energy intakes as defined in Supplemental Methods 2; and 4) were missing a baseline LDL-C measurement. In the subset cohort analysis (part B), participants were further excluded if they were missing (n = 5) a valid mandatory baseline 24-hour dietary assessment. After exclusions, 194,554 and 64,044 individuals were assessed for dietary patterns in parts A and B of the study, respectively (Supplemental Figure 1).

Participants were included in the study if they met criteria for a LCHF or standard diet (SD). A LCHF diet was defined in accordance with the Scientific Statement from the National Lipid Association Nutrition and Lifestyle Task Force[5,6] as consumption of <100 g and/or <25% TDE intake of carbohydrates and >45% TDE fat. A SD was described as any diet not meeting the above criteria. Each LCHF participant was age- and sex-matched 1:4 to individuals on a SD. In sensitivity analyses, VLC and LC diets were defined as <50 g and <100 g carbohydrates/day, respectively.

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE EVENTS. Outcomes were determined using hospital admissions linked to the UKBB. MACE or composite incident ASCVD events were defined as unstable angina, myocardial infarction, ischemic stroke, peripheral arterial disease, and coronary and carotid revascularization based on the International Classification of Diseases and Related Health Problems-10th Revision (ICD-10) diagnosis codes (Supplemental Table 1). Incident ASCVD events were determined by hospital admissions from electronic health records between the enrollment date and the end of follow-up (September 30, 2021). Events were censored on the date of loss to follow-up, death, or if individuals remained event-free up to September 30, 2021. Events occurring prior to assessment were identified by self-reported medical history. Coronary and carotid revascularization procedures were assessed using medical history and postenrollment operation OPCS-4 codes (Supplemental Table 1).

DEFINITIONS OF MONOGENIC AND POLYGENIC HYPERCHOLESTEROLEMIA. Genotyping array and exome sequencing data from the UKBB were used to identify individuals with monogenic hypercholesterolemia or polygenic hypercholesterolemia. Detailed definitions of familial hypercholesterolemia (FH)-causing variants and LDL-C polygenic risk scores (PRS) are found in Supplemental Methods 3.

STATISTICAL ANALYSES. Statistical analyses, including primary and secondary endpoints between LCHF and SD groups and comparisons of differences in lipids and incident MACE, along with sensitivity analyses, are described in Supplemental Methods 4. The interaction analysis between diet and LDL-PRS is detailed in Supplemental Methods 5.

RESULTS

PATIENT CHARACTERISTICS, DIETARY PATTERNS, AND ASSOCIATION WITH LIPID LEVELS AND ASCVD. To maximize the number of individuals available for analysis, we first included all patients who had completed at least 1 24-hour dietary questionnaire at any point in time during the study period (Supplemental Figure 1A). This resulted in 2,034 individuals on a LCHF diet and 8,136 age- and sex-matched SD controls. The patients' characteristics are shown in Supplemental Tables 2 and 3. The mean age (53.3 ± 7.6 years) and female sex percentage (71.5%) were similar in both groups with a majority of the cohort being of White British descent. LCHF participants were more likely to have diabetes (2.3% vs 1.6%, $P = 0.043$), obesity (24.6% vs 18.7%, $P < 0.001$), and had a higher body mass index (BMI) (27.5 ± 4.8 kg/m^2 and 26.4 ± 4.7 kg/m^2, $P < 0.001$). No significant differences were observed in the prevalence of hypertension, personal or family history of CVD, or exercise.

Dietary patterns were assessed for both groups (Supplemental Table 4). As expected, LCHF participants reported a lower TDE intake, had significantly lower consumption of carbohydrates (22.7% ± 8.5% vs 50.2% ± 9.3%, $P < 0.001$), increased dietary fat (52.1% ± 5.7% vs 31.3% ± 7.5%, $P < 0.001$), and protein intake (22.7% ± 6.8% vs 15.9% ± 4.1%, $P < 0.001$) as compared to SD individuals.

We next assessed the association between a LCHF diet and lipid levels (Supplemental Table 5A). Patients on a LCHF diet had significantly higher levels of LDL-C (3.71 ± 0.84 mmol/L vs 3.62 ± 0.82 mmol/L), non-high-density lipoprotein (HDL) (4.37 ± 1.05 mmol/L vs 4.28 ± 1.03 mmol/L), and apoB concentrations (1.06 ± 0.24 g/L vs 1.03 ± 0.23 g/L) compared to SD ($P < 0.001$), with an increase in prevalence of severe hypercholesterolemia, defined as LDL-C >5.0 mmol/L or apoB >1.45 g/L (7.3% vs 5.7%, $P = 0.006$, and 6.4% vs 5.1%, $P = 0.028$, respectively).

We next determined the association between a LCHF dietary pattern and risk of ASCVD events in the entire cohort (Supplemental Table 5B). The incidence of MACE was significantly greater in individuals on a LCHF diet than SD (6.3% vs 5.0%, $P = 0.015$) with a higher risk of MACE after adjustment for cardiovascular risk factors (CV RFs), ethnicity, household income, and education (adjusted HR: 1.31, 95% CI: 1.07-1.60, $P = 0.008$).

TABLE 1 Baseline Characteristics of UK Biobank Study Population on the Low-Carbohydrate High-Fat Dietary Pattern and Standard Diet in Participants With Concurrent Baseline Dietary Assessment and Blood Samples

	SD (n = 1,220)	LCHF (n = 305)	*P* Value
Sex			
Male	328 (26.9%)	82 (26.9%)	1.00
Female	892 (73.1%)	223 (73.1%)	
Age (y)	53.9 ± 7.8	53.9 ± 7.8	1.00
Ethnicity*			**0.012**
White, British/Irish/other	1147 (94.0%)	274 (89.9%)	
Black, Caribbean/African/other	20 (1.7%)	15 (4.9%)	
South Asian-Indian/Pakistani/other	30 (2.4%)	5 (1.7%)	
Chinese	4 (0.3%)	3 (1.0%)	
Mixed	10 (0.9%)	4 (1.0%)	
Others	5 (0.4%)	3 (1.0%)	
Average household income*			0.25
US$ ≤63,028	720 (59.1%)	168 (55.5%)	
US$ ≥63,029	359 (29.5%)	106 (35%)	
Missing/does not know/prefers not to answer	139 (11.4%)	29 (9.6%)	
Highest educational attainment			0.25
College/university degree	484 (39.7%)	130 (42.6%)	
A/AS levels	165 (13.5%)	45 (14.8%)	
O levels/GCSE/CSE or vocational qualification	470 (38.2%)	97 (31.7%)	
None of the above	101 (8.2%)	33 (10.8%)	
Baseline CVD risk factors			
Diabetes	21 (1.7%)	15 (4.9%)	**0.001**
Hypertension	206 (16.9%)	51 (16.7%)	0.94
BMI, kg/m^2	26.7 ± 4.8	27.7 ± 5.1	**0.002**
Obesity	241 (19.8%)	80 (26.3%)	**0.012**
Current smoking status	94 (7.7%)	32 (10.6%)	0.11
PHx CVD	12 (1.0%)	6 (2.0%)	0.20
FHx CVD	494 (40.6%)	107 (35.1%)	0.077
Physical activity, min/week	123.7 ± 91.4	116.4 ± 84.1	0.20
IPAQ physical activity group*/†			0.80
Low	158 (15.4%)	44 (16.9%)	
Moderate	447 (43.5%)	112 (42.9%)	
High	422 (41.1%)	105 (40.2%)	

Values are n (%) or mean ± SD. *Numbers of participants vary depending on available data for each subgroup. †Description of IPAQ physical groups can be found in Supplemental Table 3.

A/AS = Advanced subsidiary; BMI = body mass index; FHx CVD = family history of cardiovascular disease; GCSE = general certificate of secondary school; HNC/D = higher national certificate or diploma; HND = high national diploma; IPAQ = international physical activity questionnaire; LCHF = low-carbohydrate high-fat diet; O = ordinary; PHx CVD = personal history of cardiovascular disease; SD = standard diet; Vocational qualifications include NVQ = national vocational qualification.

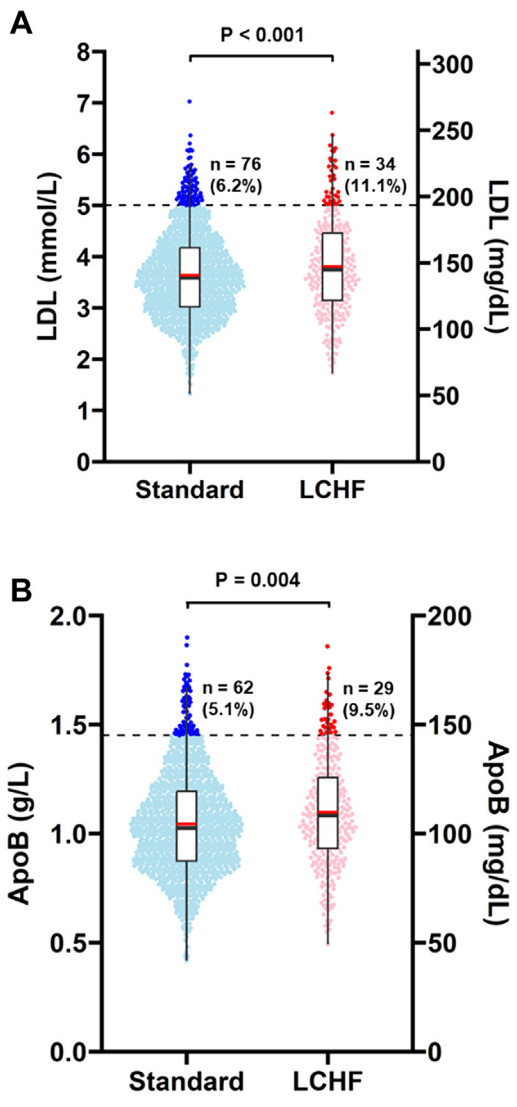
ANALYSIS OF DIETARY PATTERNS, LIPID LEVELS AND ASCVD IN INDIVIDUALS WITH A CONCURRENT DIETARY ASSESSMENT AND BLOOD SAMPLES. Subset cohort characteristics. To allow more precise temporal comparison between dietary patterns and lipid levels and subsequent ASCVD risk, we next examined a more restrictively defined cohort, which required that participants complete a 24-hour dietary assessment at the time of enrollment and concurrent with serum collection for lipid levels (Supplemental Figure 1B). This cohort consisted of 305 participants on a LCHF diet and 1,220 age- and sex-matched individuals on a SD (Table 1). Participants characteristics were similar to the previous entire cohort analysis. After matching, mean age (53.9 ± 7.8 years) and female sex percentage (73.1%) were comparable in both groups. There were no significant differences in educational, income levels, or physical activity among dietary groups (Table 1). Participants on a LCHF diet were more likely to have diabetes (4.9% vs 1.7%, $P = 0.001$), be obese (26.3% vs 19.8%, $P = 0.012$), or have a higher BMI (27.7 ± 5.1 kg/m^2 and 26.7 ± 4.8 kg/m^2, $P = 0.002$).

Dietary patterns. Participants in the LCHF group had lower TDE intake at baseline (Table 2). They had significantly lower consumption of carbohydrates as compared to SD participants (mean TDE, 23.2% ± 8.8% vs 51.0% ± 9.5%, $P < 0.001$) and a substantial increase in total fat consumption (52.3% ± 6.2% vs 30.7% ± 7.7%, $P < 0.001$), with markedly increased saturated fat (SFA) content (17.4% ± 4.3% vs 11.2% ± 3.8%) and animal fat (33.2% ± 11.9% vs 16.8% ± 7.0%, $P < 0.001$). Similarly, their dietary energy from protein intake was significantly elevated (22.2% ± 6.3% vs 15.8% ± 4.2%, $P < 0.001$), particularly animal-based protein (17.8% ± 7.5% vs 10.2% ± 4.6%, $P < 0.001$). Dietary cholesterol was also significantly higher in the LCHF group versus controls (490 ± 370 mg/day vs 200 ± 170 mg/day, $P < 0.001$).

Association between a low-carbohydrate high-fat dietary pattern and lipid levels. Patients on a LCHF diet had significantly higher levels of ketones, as defined by acetoacetate, acetone, and β-hydroxybutyrate ($P < 0.001$) (Table 3), but, as expected, below levels indicative of nutritional ketosis.[7] Mean levels of total cholesterol (6.08 ± 1.2 mmol/L vs 5.85 ± 1.1 mmol/L), LDL-C (3.81 ± 0.9 mmol/L vs 3.64 ± 0.8 mmol/L), HDL-C (1.62 ± 0.4 mmol/L vs 1.56 ± 0.4 mmol/L), non-HDL (4.46 ± 1.2 mmol/L vs 4.29 ± 1.0 mmol/L), and apoB (1.10 ± 0.25 g/L vs 1.04 ± 0.23 g/L) were all significantly higher in LCHF individuals compared to those on a SD ($P < 0.005$), whereas Lp(a) and triglycerides were lower in those on a LCHF diet (39.43 ± 44.4 nmol/L vs 46.13 ± 50 nmol/L, $P = 0.04$ and 1.34 ± 0.7 vs 1.53 ± 0.8, $P < 0.001$, respectively, Table 3). Comparison of LDL-C and apoB distributions (Figure 1) revealed that severe hypercholesterolemia (LDL-C >5.0 mmol/L and apoB >1.45 g/L) was nearly twice as common in LCHF participants than SD (11.1% vs 6.2%, $P < 0.001$, and 9.5% vs 5.1%, $P = 0.004$, respectively).

Low-carbohydrate high-fat diet and atherosclerotic cardiovascular disease. We next examined the association between a LCHF dietary pattern and risk of ASCVD events (Figure 2). Over a mean follow-up time

FIGURE 1 LDL-Cholesterol and Apolipoprotein B Distributions According to Diet



(A) LDL-C and (B) apoB distributions according to LCHF diet and standard diet. Boxplots display the mean (red line) and median (black line). Dotted thresholds indicate severe hypercholesterolemia (LDL-C >5.0 mmol/L or apo B >1.45 g/L), which was significantly more frequent in LCHF participants than those on SD. ApoB = apolipoprotein B; LCHF = low-carbohydrate high-fat diet; LDL-C = low-density lipoprotein-cholesterol; SD = standard diet.

of 11.8 years, the incidence of MACE was greater in individuals on a LCHF diet than SD (9.8% vs 4.3%, $P < 0.001$). Using Cox proportional hazard regression adjusted for diabetes, smoking, hypertension, and BMI, patients following a LCHF diet had a more than 2 times higher risk of MACE than those on SD (HR: 2.18, 95% CI: 1.39-3.43, $P < 0.001$).

To further explore the relationships between diet, lipid levels, and cardiovascular risk, we stratified patients from the subset cohort by bins of LDL-C (<3.5, ≥3.5-5.0, ≥5.0 mmol/L) and diet (**Figure 3**). When compared to the reference group following a SD with LDL-C<3.5 mmol/L, cardiovascular risk increased according to both the LCHF diet and the LDL-C bin. The greatest risk was observed in individuals with severe hypercholesterolemia (LDL ≥5.0 mmol/L) on a LCHF diet (HR: 6.68, 95% CI: 2.62-17.09, $P < 0.001$).

Subgroup and sensitivity analyses based on variations of low-carbohydrate diets. To examine how variation in different definitions of LC diets influenced these results, we performed a series of sensitivity analyses (Supplemental Table 6) in participants with at least 1 dietary assessment collected concurrently with plasma lipid levels. We observed similar significant numerical and directional trends in rates of MACE between control and carbohydrate-restricted groups using a restriction in carbohydrates to <100 g/day and <50 g/day with no inclusion of dietary fat. Rates of incident ASCVD events (8.1% vs 5.2%, $P < 0.001$ and 7.8% vs 3.6%, $P = 0.07$) and cardiovascular risk (HR: 1.50, 95% CI: 1.16-1.94, $P = 0.002$, and HR: 2.05, 95% CI: 0.84-4.97, $P = 0.08$), adjusted for CV RFs, were greater in both carbohydrate-restricted groups, respectively, compared to individuals on SD.

Given the increased prevalence of diabetes in the LCHF group, we also excluded diabetic participants to account for this potential confounding factor. After this exclusion, incidence of ASCVD continued to be more frequent in the LCHF group (8.3% vs 4.1%, $P = 0.004$), and this association remained significant after adjusting for major CV RFs (HR: 2.01, 95% CI: 1.23-3.29, $P = 0.005$) (Supplemental Table 6). Similarly, inclusion of individuals on lipid-lowering therapy showed a MACE incidence of 11.8% in those on LCHF compared to 7.3% in controls ($P = 0.006$) with a slightly attenuated HR: 1.52 (95% CI: 1.06-2.18, $P = 0.027$).

To assess the persistence of LCHF dietary patterns (intermittently or consistently), we further examined individuals who had completed ≥2 dietary 24-hour questionnaires between 2011 and 2012, including the enrollment survey. Participants' baseline characteristics, CV RFs, lipid levels, and risk of ASCVD events are summarized in Supplemental Table 7. Mean age (53.8 ± 7.3 years) and female sex percentage (77.8%) were similar in both groups. Participants on a LCHF diet having completed ≥2 dietary questionnaires were more likely to be overweight compared to individuals on SD (BMI 27.4 ± 5.5 kg/m^2 vs 25.7 ± 4.3 kg/m^2,

TABLE 2 Estimated Nutrients From at Least 1 24-Hour Dietary Intake in Participants With Concurrent Baseline Dietary Assessment and Blood Samples

Nutritional Factors	Standard Diet (n = 1,220)		LCHF (n = 305)		*P* Value, % TDE
	% TDE	g/day	% TDE	g/day	
Total daily energy (TDE) intake, kcal/d	1,992.1 ± 604.8	–	1,449.9 ± 650.1	–	<0.001
Carbohydrate intake	51.0 ± 9.5	252.5 ± 85.7	23.2 ± 8.8	78.9 ± 36.8	<0.001
Free sugar	11.8 ± 6.7	59.9 ± 40.7	4.9 ± 4.7	17.4 ± 17.1	<0.001
Protein intake	15.8 ± 4.2	76.8 ± 25.7	22.2 ± 6.3	79.6 ± 37.9	<0.001
Animal protein	10.2 ± 4.6	49.2 ± 23.2	17.8 ± 7.5	63.6 ± 35.7	<0.001
Plant protein	5.6 ± 1.8	27.7 ± 11.5	4.3 ± 2.4	16.0 ± 12.6	<0.001
Total fat intake	30.7 ± 7.7	69.1 ± 29.5	52.3 ± 6.2	84.6 ± 39.3	<0.001
Animal fat	16.8 ± 7.0	37.9 ± 20.8	33.2 ± 11.9	52.8 ± 29.4	<0.001
Plant fat	13.9 ± 6.0	31.2 ± 17.0	19.1 ± 12.7	31.7 ± 27.7	<0.001
Total saturated fat	11.2 ± 3.8	25.4 ± 12.7	17.4 ± 4.3	27.8 ± 13.6	<0.001
Cholesterol intake	0.098 ± 0.07	0.2 ± 0.17	0.31 ± 0.22	0.49 ± 0.37	<0.001
Alcohol intake	5.1 ± 7.5	14.8 ± 22.4	3.9 ± 6.2	11.0 ± 20.1	0.004

Values are mean ± SD.
LCHF = low-carbohydrate high-fat diet; SD = standard diet; TDE = total daily energy intake.

P = 0.03), similar to previous findings in individuals having completed at least 1 survey (Supplemental Tables 2 and 7A, **Table 1**). No significant differences were observed in prevalence of diabetes, hypertension, smoking, personal or family history of CVD.

Similar to previous findings, consumption of a LCHF diet was associated with significantly higher levels of total cholesterol (6.13 ± 1.25 mmol/L vs 5.69 ± 1.06 mmol/L), LDL-C (3.86 ± 0.97 mmol/L vs 3.49 ± 0.83 mmol/L), non-HDL (4.43 ± 1.08 mmol/L vs 4.08 ± 1.03 mmol/L), and apoB (1.1 ± 0.26 g/L vs 1.01 ± 0.24 g/L) compared to SD ($P < 0.05$). Furthermore, severe hypercholesterolemia remained significantly more frequent in LCHF participants compared to controls (LDL-C >5.0 mmol/L, 17.0% vs 5.1%, $P = 0.003$, and apoB >1.45 g/L, 13.0% vs 4.2%, $P = 0.014$) (Supplemental Table 7B). Incident ASCVD events (5.6% vs 2.8%, $P = 0.31$) and adjusted cardiovascular risk (HR: 1.99, 95% CI: 0.49-8.14, $P = 0.34$) also tended to be greater in the LCHF group, although these differences were not statistically significant (Supplemental Table 7C).

TABLE 3 Lipid Levels and Ketone Bodies on a Low-Carbohydrate High-Fat Dietary Pattern and Standard Diet in Participants With Concurrent Baseline Dietary Assessment and Blood Samples

Biochemistry	Standard Diet (n = 1,220)	LCHF (n = 305)	*P* Value
β-Hydroxybutyrate*, mmol/L	0.06 ± 0.06	0.14 ± 0.16	<0.001
Acetone*, mmol/L	0.01 ± 0.004	0.02 ± 0.017	<0.001
Acetoacetate*, mmol/L	0.01 ± 0.01	0.02 ± 0.02	<0.001
Total cholesterol, mmol/L	5.85 ± 1.1	6.08 ± 1.2	0.002
LDL-C, mmol/L	3.64 ± 0.8	3.81 ± 0.9	0.004
HDL-C, mmol/L	1.56 ± 0.4	1.62 ± 0.4	0.039
Non-HDL, mmol/L	4.29 ± 1.0	4.46 ± 1.2	0.03
Apolipoprotein B, g/L	1.04 ± 0.23	1.10 ± 0.25	<0.001
Lipoprotein(a), nmol/L	46.13 ± 50.0	39.43 ± 44.4	0.041
Triglycerides, mmol/L	1.53 ± 0.8	1.34 ± 0.7	<0.001
HbA1c, %	5.33 ± 0.4	5.37 ± 0.6	0.337
Glucose, mmol/L	5.05 ± 0.7	5.16 ± 0.8	0.05

Values are mean ± SD. For total cholesterol, HDL-C, LDL-C, and non-HDL-C, to convert from mmol/L to mg/dL, multiply by 38.670. For apolipoprotein B, to convert from g/L to mg/dL, multiply by 100. For triglycerides, to convert from mmol/L to mg/dL, multiply by 88.574. *Measurement of ketone bodies (β-hydroxybutyrate, acetone, and aceotoacetate) was performed by nuclear magnetic resonance. Based on sample availability, n = 278 participants on SD and n = 70 on LCHF.
apoB = apolipoprotein B; HbA1c = hemoglobin A1c; HDL-C = high-density cholesterol; LDL-C = low-density lipoprotein-cholesterol; non-HDL = non-high-density lipoprotein cholesterol.

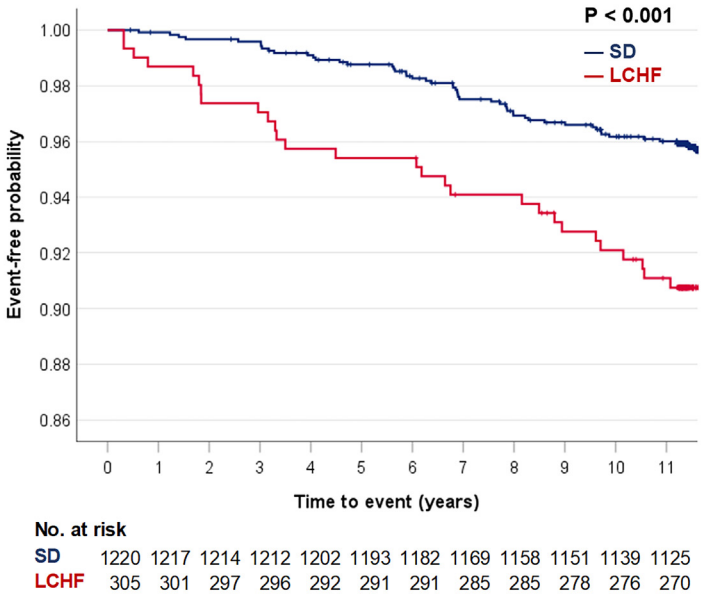
LDL-cholesterol levels based on polygenic risk scores and dietary patterns. We next examined if genetic variants associated with hypercholesterolemia influenced the response to diet and could explain potential interindividual variations in lipid levels among individuals consuming a LCHF diet. The subset cohort of participants with concurrent dietary assessment with serum lipid levels was used. No monogenic FH-causing variants were identified in the LCHF group, while 6 participants on SD had pathogenic/likely-pathogenic FH-causing variants (Supplemental Table 8). This indicates that an excess in the prevalence of FH does not explain the higher frequency of severe hypercholesterolemia among individuals consuming a LCHF diet. An elevated LDL-PRS (≥80th percentile) was present in 93 (30.5%) LCHF individuals and 330 (27.0%) SD participants

FIGURE 2 Risk of MACE in Participants on a LCHF Diet and Standard Diet

A

	Standard Diet (n = 1220)	LCHF (n = 305)	*P*-value
Incident ASCVD events			
ASCVD, n (%)	53 (4.3%)	30 (9.8%)	**< 0.001**
No ASCVD, n (%)	1167 (95.7%)	275 (90.2%)	
Co-variates	**Adjusted HR**	**95% CI**	***P*-value**
Risk of ASCVD events on LCHF diet	**2.18**	1.39 - 3.43	**< 0.001**
Diabetes	3.37	1.53 - 7.39	**0.002**
Current smoking	2.44	1.37 - 4.34	**0.002**
Hypertension	1.89	1.14 - 3.14	**0.013**
BMI	1.02	0.98 - 1.06	0.383

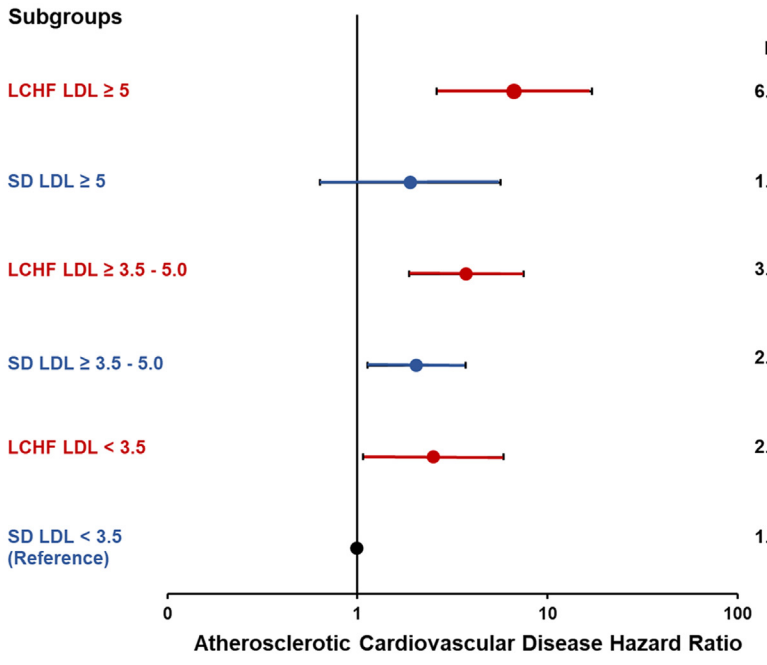
B



(A) Upper panel: proportion of incident ASCVD events in participants on both diets. (A) Lower panel: risk of ASCVD events assessed with Cox regression model adjusted for diet, diabetes, smoking, hypertension, and BMI. (B) Kaplan-Meier curves for time to ASCVD events stratified by diet: x-axis, time since first assessment and completion of initial 24-hour dietary questionnaire; y-axis, event-free probability.
ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; HR = hazard ratio; LCHF = low-carbohydrate high-fat diet; SD = standard diet.

(Figure 4). Mean LDL-C levels were significantly greater in the LCHF vs SD group among participants with a high LDL-C PRS (4.38 ± 1.2 mmol/L vs 3.85 ± 0.9 mmol/L, $P < 0.0001$) (Supplemental Table 9), whereas there was no significant difference in LDL-C concentrations in subjects with a non-high LDL-C PRS (3.55 ± 0.6 mmol/L vs 3.56 ± 0.8 mmol/L, $P = 0.93$). Consistent with this, severe hypercholesterolemia was 3-times more prevalent in participants with an elevated LDL-C PRS on a LCHF than in those on a SD (32.3% vs 10.6%, $P < 0.0001$) (Figure 4). This prevalence did not significantly differ by diet among those with a non-high LDL-C PRS (1.9% vs 4.6%, $P = 0.07$). These findings suggest that severe

FIGURE 3 ASCVD Risk According to LDL-Cholesterol and Dietary Pattern



Participants were stratified by bins of LDL-C (LDL-C <3.5, ≥3.5-5.0, ≥5.0 mmol/L) and dietary pattern, with individuals on standard diet with LDL-C <3.5 mmol/L representing the reference group. HRs are plotted on a logarithmic scale. Abbreviations as in Figure 1.

hypercholesterolemia in participants consuming a LCHF diet is most likely to occur in individuals with a background elevated LDL-C PRS.

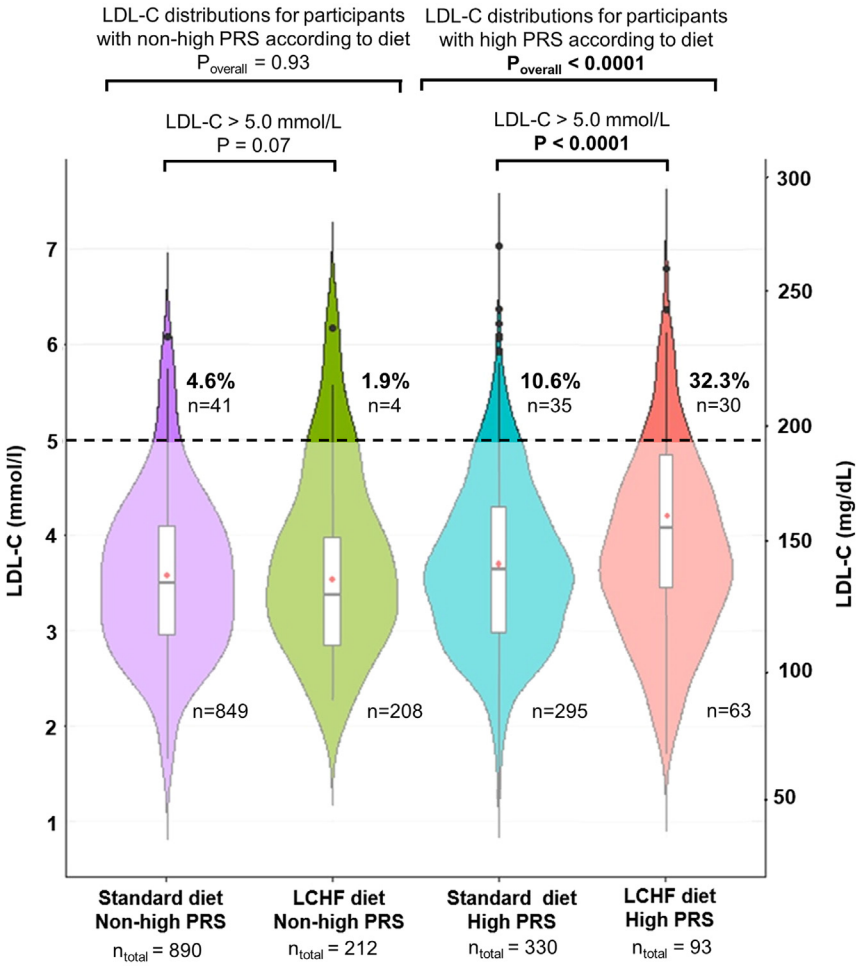
Given the observation of an apparently greater effect of diet on LDL-C in individuals with an elevated PRS, we formally tested for an interaction between dietary pattern and PRS using a multivariable regression model. This revealed a significant interaction between diet and PRS, such that the effect of a LCHF diet on LDL-C levels was significantly greater in those with an elevated vs nonelevated PRS ($\beta = 0.73$ [95% CI: 0.50-0.96], $P_{interaction}<0.001$) (Supplemental Table 10).

DISCUSSION

In this prospective cohort study, consumption of a self-reported diet low in carbohydrates (<25% TDE and/or <100 g/day) and high in fat (>45% TDE) was associated with increased LDL-C and apoB levels and a greater risk of incident MACE after adjustment for CV RFs (**Central Illustration**). Severe hypercholesterolemia was nearly twice as common in individuals on a LCHF diet than SD, and the cardiovascular risk associated with a LCHF dietary pattern was greater in individuals with LDL-C levels >5.0 mmol/L. These results were consistent in a larger cohort designed to maximize the number of observations and a more restrictive cohort that required concurrent dietary surveys and lipid levels. The findings were also robust to different variations in degree of carbohydrate restriction, and the changes in lipid levels persisted among participants with ≥2 dietary surveys with directionally similar associations with MACE. A significant interaction between an LDL-C PRS and LCHF diet was also detected, such that individuals with an elevated LDL-C PRS had higher LDL-C concentrations on a LCHF diet as compared to those with a low PRS (**Central Illustration**).

After exclusions and matching, our study comprised a cohort of 2034 individuals meeting LCHF diet criteria with at least 1 dietary assessment at any point after enrollment and a subset cohort of 305 LCHF participants with concurrent dietary recall questionnaires and blood tests at initial visit. UKBB participants were recruited between 2006 and 2010, at a time where LCHF dietary patterns were not as

FIGURE 4 LDL-Cholesterol Distributions Based on Polygenic Risk Scores and Dietary Patterns



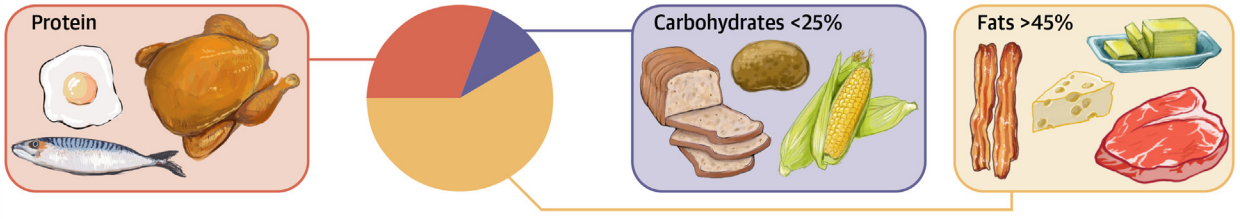
Violon plots represent LDL-C distributions based on high vs non-high LDL-PRS and dietary patterns: mean (red dot), median (black line), black dots (participants with significantly high LDL-C), dotted threshold line (severe hypercholesterolemia with LDL ≥5.0 mmol/L).
PRS = polygenic risk score; other abbreviations as in Figure 1.

prevalent, as evidenced by the growing number of PubMed publications in the last decade (107 in 2010 compared to 624 in 2023).[15] The prevalence of females in our cohort (73.1%) aligns with dieting studies that demonstrate sex and gender differences in personal priorities related to physical health, dietary trends, and nutrition beliefs[2,16] with more females prioritizing weight management and improvement in diets than males. As anticipated, diabetes and obesity were more common in individuals reporting a LCHF diet, in accordance with common perceptions that this dietary pattern is beneficial in managing these conditions. However, the reasons why certain individuals chose to pursue a LCHF diet are unknown, which could introduce both measured and unmeasured confounding. While the association with MACE remained significant after adjustments for diabetes and obesity, there is likely to be residual confounding.

Individuals reporting a LCHF diet had a lower TDE intake at baseline compared to the SD group. This is in agreement with previous observations that LC diets may trigger satiety hormones and suppress appetite, leading to a reduction in caloric intake.[5,17] As expected, LCHF participants had limited consumption of carbohydrates in favor of a significant increase in intake of fats and protein, rich in animal-based content. TDE from fat was considerably elevated, with

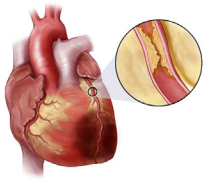
CENTRAL ILLUSTRATION **Association of a LCHF Dietary Pattern With Hypercholesterolemia and Increased Risk of ASCVD**

Low Carbohydrate High Fat (LCHF) Diet

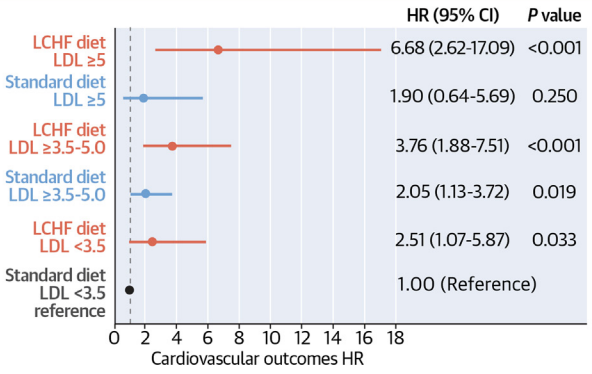


Risk of Atherosclerotic Cardiovascular Disease (ASCVD) Events

LCHF diet associated with a **2.2-fold increased** risk of incident ASCVD events

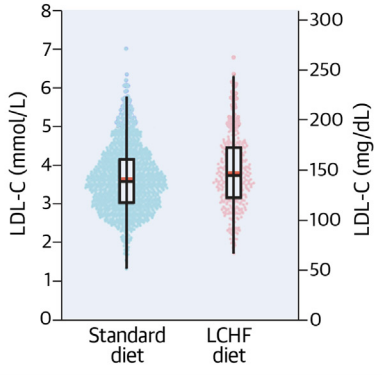


	Standard diet (n=1,220)	LCHF diet (n=305)	*P* value
Incident ASCVD n (%)	53 (4.3%)	30 (9.8%)	<0.001
Adjusted risk of ASCVD	HR 2.18	95% CI 1.39-3.43	<0.001



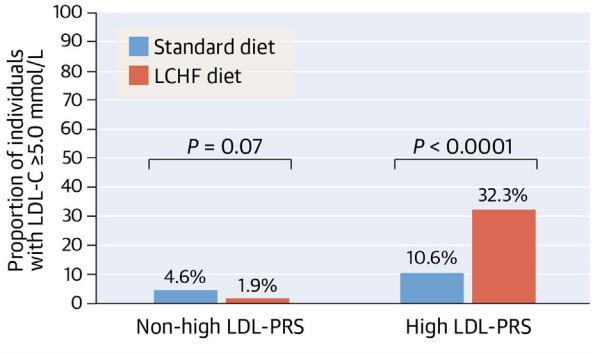
LDL-Cholesterol

LCHF diet associated with higher levels of LDL-C and apoB levels



LDL Polygenic Risk Score

Individuals with elevated LDL-PRS have the highest LDL-C levels on a LCHF diet



Iatan I, et al. JACC Adv. 2024;3(6):100924.

Consumption of a LCHF diet was associated with significantly higher LDL-C and apoB levels, with severe hypercholesterolemia (LDL ≥5.0 mmol/L) being twice as frequent in individuals on a LCHF diet. Incidence of ASCVD events was significantly greater in LCHF participants than those on a standard diet. Consumption of this dietary pattern was associated with a 2.2-fold increased ASCVD risk after adjustment for cardiovascular risk factors. The highest cardiovascular risk was observed in individuals with LDL-C ≥5.0 mmol/L on a LCHF diet. Participants with an elevated LDL-PRS had the highest LDL-C on as carbohydrate-restrictive diet, with severe hypercholesterolemia being 3 times more frequent in these individuals. Abbreviations as in Figure 1 and 2.

higher consumption of animal sources and a marked component from SFA. Multiple clinical trials support the causal link between SFA intake and increased LDL-C levels, a firmly established risk factor for ASCVD. Kelly et al[18] investigated the relationship between different macronutrients and serum lipids in the UKBB (n = 24,639). Their analyses demonstrated that fat from animal sources, and particularly SFA intake, was positively associated with LDL-C and apoB concentrations, in agreement with previous randomized controlled trials and observational studies.[19] In a meta-analysis from the Atherosclerosis Risk in Communities study (n = 432,179), when carbohydrates were exchanged for animal-derived fat or protein, the associated mortality risk increased by 18%, whereas it decreased by 18% when the substitutions were plant-based.[20] Dietary cholesterol consumption was also 2-fold higher in LCHF individuals as compared to SD (~490 vs ~200 mg/d). The American College of Cardiology/American Heart Association (ACC/AHA) Prevention and Dietary[21,22] guidelines recommend <200 mg/day of dietary cholesterol and <7% calories from SFA to decrease ASCVD risk.

We observed significant elevations in ketone bodies in LCHF individuals. In support of this, a recent study from Multi-Ethnic Study of Atherosclerosis found significant associations between elevated circulating ketone bodies and a higher rate of CVD and mortality.[23] As expected, however, due to the LCHF dietary definition we used, β-hydroxybutyrate levels were below a range compatible with nutritional ketosis, defined as 0.5 to 3.0 mmol/L.[7] Nevertheless, this finding suggests that our approach to identify participants consuming LCHF was appropriate and selected for individuals with expected metabolic changes induced by carbohydrate restriction. Furthermore, although our study did not evaluate the direct impact of KDs on cardiovascular risk, in sensitivity analyses, a numerical and directional trend in MACE was observed between controls and <50 g/day carbohydrate-restricted groups.

We found that levels of LDL-C, non-HDL, and apoB were significantly elevated in the LCHF group (**Central Illustration**). Interestingly, although the differences in mean LDL-C and apoB concentrations between both groups were relatively modest in magnitude, the probability of having severe hypercholesterolemia was nearly double in LCHF participants. This suggests that, rather than influencing LDL-C levels similarly in everyone, consumption of a LCHF dietary pattern leads to substantial elevations in LDL-C in a subset of individuals. Indeed, our results indicate that this is most likely to occur in individuals with a genetic propensity toward hypercholesterolemia, as reflected by an elevated LDL-C PRS. This may help explain the observed clinical heterogeneity in lipid level responses among individuals on carbohydrate-restricted diets encountered in clinical practice.[8-13]

In contrast to the increase in LDL-C and apoB, we observed lower Lp(a) and triglyceride concentrations in those consuming a LCHF diet, in agreement with prior studies.[24] The fact that rates of ASCVD events were higher in the LCHF group suggests that the reduction in Lp(a) and triglycerides was not sufficient to offset the rise in LDL-C and apoB.

Previous studies have reported lower, higher, or similar apoB or LDL-C[5,6,8-12,24,25] levels in individuals consuming a LCHF diet. These conflicting findings may be due to study design, short duration of observation, and lack of uniform diet composition, reflecting variations in quantity and quality of carbohydrate and fat intake. Differences in diet adherence and variation in weight loss in response to diet may further influence these results.[5,6] Our findings are in agreement with prior studies reporting LDL-C increases on VLC/LCHF diets in different populations, including normal-weight individuals,[8-12] ultra-endurance athletes,[9] and young healthy females.[25]

Previous case studies have suggested that in susceptible individuals, LCHF diets may unmask genetically-influenced dyslipidemias. Gene-nutrient interaction studies demonstrate that genetics contribute to interindividual variability in lipoprotein responses to dietary interventions.[13] Goldberg et al[10] described 5 patients with a marked response to KDs/LCHF diets, with 2 having high LDL-C PRS and 1 with an *APOE E2E2* genotype. In our study, we identified monogenic FH-causing variants in 6 individuals reporting a SD and none reporting a LCHF diet. This suggests that the greater prevalence of severe hypercholesterolemia among LCHF individuals is not explained by a greater frequency of FH. In contrast, we observed a marked effect of the LDL-C PRS, such that significantly increased LDL-C levels were found in individuals on a LCHF diet with a high PRS but not with a normal PRS. This was further confirmed by a statistically significant interaction between diet and PRS, whereby there was a significant effect of the LCHF diet on LDL-C levels. These results suggest that an elevated LDL-C PRS may contribute to the development of severe hypercholesterolemia in response

to a LCHF diet and highlight the potential role of genetic profiling to predict an individual's response to this dietary pattern.

To our knowledge, this is one of the first studies to demonstrate a relationship between LCHF dietary patterns, increased lipids, and elevated ASCVD risk. There are limited data reporting cardiovascular outcomes on carbohydrate-restrictive dietary patterns. In the CARDIA study,[26] LC intake was associated with an elevated risk of coronary artery calcium progression over 8.3 years, particularly when animal fat replaced carbohydrates. In line with this, Lagiou et al[27] found that LC dietary consumptions were associated with increased CVD risk in 43,396 Swedish females followed for 15.7 years. Similarly, results from NHANES and 9 other prospective cohort studies (n = 462,934, 16.1-year follow-up) also found that participants with the lowest carbohydrate intake (<39% TDE) had the highest risk of overall mortality and CVD death.[28]

In support of these findings, the recent AHA Scientific Statement on 10 popular dietary patterns raised caution with respect to LC/VLC diets, placing them in the last tiers based on their alignment with the 2021 AHA Dietary Guidelines.[29] For individuals following these diets, animal-sourced foods tended to be overemphasized, leading to inappropriate restriction of fiber, heart-healthy nutrients, and increased SFA intake. This reinforced previous recommendations that adults should consume a healthy plant-based or Mediterranean-like diet, limiting dietary patterns that focus on LC and a high intake of animal fat that are associated with increased cardiac and noncardiac mortality.[21,29]

STRENGTHS AND LIMITATIONS. This study has strengths and limitations that merit consideration. First, due to its observational nature, a causal relationship between LCHF diets and MACE cannot be inferred. Despite adjustments for known confounders, residual confounding cannot be ruled out. Importantly, diabetes was more common in individuals reporting a LCHF diet; however, the association with MACE remained significant even after excluding diabetic participants. Our study design also mitigated against the possibility of reverse causality by focusing on incident ASCVD events that occurred after dietary assessment and adjusting for CV RFs. Second, a subset of this study was based on at least 1 24-hour dietary baseline assessment performed at the time when lipid levels were collected. This approach has the strength of allowing temporal comparison to blood markers, as subsequent web-based questionnaires did not coincide with repeat blood samples, although it is possible that individual dietary patterns changed throughout the course of the study. The Oxford WebQ dietary questionnaire, while being a validated instrument used in many large prospective studies14, is prone to measurement error and recall bias, and is a short-term assessment of dietary pattern which may not accurately reflect longer term food intake. We confirmed similar significant changes in lipid levels among individuals who reported consuming a LCHF diet at any point after enrollment in a larger cohort of 2034 individuals and on ≥2 dietary surveys, with directionally similar associations with MACE. Although the association with MACE was not statistically significant in the ≥2 subgroup analysis, this may relate to the smaller sample size. Third, participants in the UKBB tend to be healthier than the general population, with lower LDL-C levels, which may have deflated MACE risk estimations. Lastly, the UKBB is predominantly composed of individuals of White/European ancestry, and generalizability of these findings to other ethnic groups requires further research.

CONCLUSIONS

In a population-based cohort, self-reported consumption of a LCHF diet was associated with increased levels of LDL-C and apoB and an increased risk of incident atherosclerotic cardiovascular events. These findings highlight the potential cardiovascular risk of this dietary pattern and suggest that hypercholesterolemia occurring during a LCHF diet should not be assumed to be benign.

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Dr Brunham has served on advisory boards for Amgen, Novartis, HLS Therapeutics, and Ultragenyx. Dr Iatan has served on advisory boards for Novartis and HLS Therapeutics and receiving honoraria from Novartis and Sanofi. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE AND PATIENT CARE 1: In certain individuals, a diet low in carbohydrates (<25% TDE and/or <100 g carbohydrates/day) and high in fat (>45% TDE) can be associated with significantly higher LDL-C and apolipoprotein B, and an increased risk of incident cardiovascular events. The cardiovascular risk associated with a LCHF dietary pattern was greater in individuals with LDL-C above >5.0 mmol/L. Close monitoring of cholesterol levels, focus on plant-based alternatives, and management of underlying CV RFs should be considered when pursuing this dietary pattern.

COMPETENCY IN MEDICAL KNOWLEDGE AND PATIENT CARE 2: The effect of a LCHF diet on lipid levels was significantly greater in individuals with an elevated LDL-C PRS, as individuals with a high LDL-C PRS had the highest concentrations of LDL-C on a LCHF diet as compared to those with a low PRS. Genetic profiling may be considered to predict an individual's response to this diet and improve our understanding of interindividual variations in response to these dietary patterns.

TRANSLATIONAL OUTLOOK: The recently published Scientific Statement from the AHA placed LC and VLC dietary patterns, including LCHF diets, on the third and fourth tiers of alignment with the 2021 AHA Dietary Guidelines. Further research is therefore needed to assess the safety and efficacy of LCHF diets and improve understanding of interindividual variations in response to these dietary patterns.

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KEY WORDS atherosclerotic cardiovascular disease, low-carbohydrate high-fat diet, hypercholesterolemia, low-density lipoprotein polygenic risk score, UK Biobank, incident major adverse cardiovascular events

APPENDIX For supplemental methods, tables, and figures, please see the online version of this paper.